REMARKS

This responds to the Office Action mailed on October 9, 2007, and the references cited therewith.

Claim 7, 8, 10 and 20 are cancelled without prejudice or disclaimer. Therefore, claims 1-3, 9, 12-17, 21 and 22 are now pending in this application.

Claims 1, 3, 21 and 22 are amended. In particular, language defining the human as infected with HIV1 has been moved from the preamble of claim 1 to the body of the claim. Claim 1 also defines the attenuated recombinant pox virus as a *NYVAC, ALVAC or MVA* pox virus. Support for use of NYVAC, ALVAC or MVA recombinant pox viruses can be found throughout the specification, for example, at page 7, line 27 to page 9, line 13 and at page 15, lines 19-20. Also, the term "proliferative" has been added to clarify that peptides are presented in an amount sufficient to stimulate HIV antigen-specific CD8+ and CD4+ proliferative responses. Support for proliferative CD8+ and CD4+ responses can be found throughout the specification, for example, at page 11, lines 23-30; page 13, lines 6-33; page 14, line 22 to page 15, line 9; and in the Examples (see, e.g., page 20, lines 25-28, page 22, lines 8-10 and page 26, lines 8-10). Claim 1 also recites that the HIV specific peptides consist of HIV Gag or Env peptides (rather than comprise HIV Gag, Gp120, Nef or Pol peptides). Support for use of Gag, Pol or Env peptides can be found throughout the specification as filed, for example, in the Examples (see, e.g., page 18, lines 28-31). In addition, the dependencies of claim 3, 21 and 22 have been changed from claim 2 to claim 1.

Applicant submits that no new matter has been added to the application.

§112, First Paragraph, Rejection of the Claims

Claims 1-3, 5-10, 12-18 and 20-22 were rejected under 35 U.S.C. § 112, first paragraph, as allegedly lacking enablement. In his response to Applicants arguments, the Examiner alleges the specification fails to enable: (1) an immunoprotective response; (2) all HIV Gag, Gp120, Nef or Pol peptides; and (3) all recombinant pox viruses. The Examiner also asserts that Applicant has failed to submit any new experimental data.

Protective Immune Response

The Examiner interprets the claims to encompass protective immune responses and asserts that development of protective immune responses against HIV infection is unpredictable and no one to date has developed a successful anti-HIV vaccine. In view of the difficulties in developing such an HIV vaccine, the Examiner concludes that Applicant's claims lack enablement.

To support his contentions, the Examiner quotes portions of the specification as alleged evidence that the claims must be interpreted to involve immunoprotective responses and use of protective vaccines. The Examiner then concludes that "the issues raised pertaining to CTL vaccine development are directly relevant."

However, it is a "bedrock principle" of patent law that "the claims of a patent define the invention to which the patentee is entitled the right to exclude." *Phillips v. AWH Corp.*, 415 F3d 1303, 1312 (Fed. Cir. 2005); *Vitronics Corp. v. Conceptronic, Inc.*, 90 F.3d 1576, 1582 (Fed. Cir. 1996) ("we look to the words of the claims themselves . . . to define the scope of the patented invention"); *Markman v. Westview Instruments, Inc.*, 52 F.3d 967, 980 (Fed. Cir. 1995) ("The written description part of the specification itself does not delimit the right to exclude. That is the function and purpose of claims.").

Accordingly, Applicant requests that the Examiner interpret the scope of the invention by reference to the claims, as required by law and not commit "one of the cardinal sins of patent law—reading a limitation from the written description into the claims." *SciMed Life Sys., Inc. v. Advanced Cardiovascular Sys., Inc.*, 242 F.3d 1337, 1340 (Fed. Cir. 2001).

Here the claims are explicitly drawn to methods that stimulate HIV antigen-specific CD8+ and CD4+ proliferative responses in humans infected with an HIV1 retrovirus, where the human has a viral load of less than 10,000 viral copies per ml of plasma and a $CD4^+$ cell count of above 500 cells/ml. Accordingly, the human is already infected with HIV1 and has existing CD4+ and CD8+ cells that recognize HIV and then proliferate in response to the administered HIV-specific peptides.

Accordingly, use of documents disclosing the difficulties of preventing HIV infection is improper because these articles do not address the substance of the claimed invention.

Moreover, Applicant submits that the practice of the invention is not so unpredictable as the Examiner has alleged. Data exists illustrating that that the present methods do reproducibly stimulate a HIV1-specific $CD4^+$ and $CD8^+$ response in humans/mammals already infected with an HIV.

Thus, the specification discloses data (FIG. 2, page 18, line 24 to page 21, line 28) showing that HAART-treated animals who were inoculated with a recombinant NYVAC, which produces gag-pol-env HIV specific peptides (Group B), exhibited substantially increased percentages of HIV-specific $CD8^+$ T cells relative to HAART-treated animals who received a placebo vaccine (Group A) or animals inoculated with the recombinant NYVAC virus who had received no HAART treatment (Group C).

The specification also provides data (e.g., FIG. 1, lower three panels) showing that greater numbers of $CD4^+$ T cells proliferate when animals receive recombinant NYVAC expressing gag, pol and env peptides (Group B) after HAART treatment than when animals are treated with HAART alone (Group A) or receive no treatment (Group C).

The Declaration by Dr. Genoveffa Franchini (in May 2005) describes the Quest trial, where patients who received the recombinant pox virus had increased CD4+ and CD8+ responses at week 24 (see page 11 of the Declaration Appendix). The results of the Quest trial with respect to increased CD4+ and CD8+ responses were confirmed by a more complete study as shown in Kimloch-de Loes et al., J. Infect. Diseases 192: 607-17 (2005) (provided in the January 7, 2008 SIDS).

Applicant has previously provided articles showing that other groups utilizing the present methods also can stimulate CD4+ and CD8+ responses. *See,* Dorrell (J. Virol. 80: 4705-16 (2006), Tubiana (Vaccine 23:4292-4301 (2005)) and Jin et al. (J. Virol. 76: 2206-16 (2002)).

Dorrell shows that methods employing the MVA.HIVA pox virus stimulated proliferation of both CD4+ and CD8+ T cells in 75% of patients (see 4714, right column, first complete paragraph).

Tubiana shows that HIV-gag-specific CD8 T cells were boosted in 55% of patients tested.

Jin shows that administration of the ALVAC vCP1452 recombinant virus stimulates an HIV1-specific $CD8^+$ response in HIV-infected patients who have been receiving antiretroviral therapy. Note that the vCP1452 recombinant virus is the same as the recombinant virus referenced in the Declaration by Dr. Genoveffa Franchini filed on May 16, 2005.

Therefore, ample data exists showing that the methods of the invention can reproducibly stimulate HIV antigen-specific CD8+ and CD4+ proliferative responses. Applicant respectfully requests withdrawal of this rejection under section 112.

New Experimental Data

Applicant further submits that the Examiner's statement that previous responses "failed to proffer any new experimental evidence of data obtained from peer-reviewed publications that addresses the aforementioned caveats" is blatantly false.

The articles by Dorrell, Tubiana, Kimloch-de Loes and Jin are not only directly relevant but are from the peer-reviewed Journal of Virology, Vaccine, Journal of Infectious Diseases, and Journal of Virology respectively. Even a cursory review of these peer-reviewed publications demonstrates that these articles describe new experimental data proving that Applicant's claimed methods reproducibly function as described in Applicant's claims and specification.

In particular, the Dorrell article discloses the following at page 4711:

This study shows that a therapeutic immunization strategy employing intradermal administration of MVA.HIVA to chronically HIV-1-infected individuals under HAART suppression is able to elicit broad, durable virus-specific $CD8^+$ and $CD4^+$ T-cell responses. The immunogenicity of recombinant MVA that we observed is particularly impressive when considering the following: (i) the study cohort comprised patients with more advanced disease (median pre-HAART CD4 T-cell nadir, 180 cells/μl) than those included in previously reported studies (19, 21, 32, 39, 40); (ii) the dose of MVA was modest compared with previous human and nonhuman primate studies (8, 16, 33, 41); and (iii) the sequence of the immunogen is based on the clade A consensus sequence (14), whereas the majority of vaccinees were known to be infected with other subtypes (data not shown). Furthermore, HIV-1 infection per se did not appear to inhibit the generation of responses to MVA.HIVA despite the potential for immune interference (36). Indeed, the rapidity of T-cell expansion after immunization and the magnitude of the peak responses, which were 10- to 100-fold greater than responses in HIV-uninfected individuals given the same vaccine (12a), suggested that the vaccine was boosting responses primed by HIV-1 itself. As

The Tubiana article states the following at page 4297:

> During the immunization phase, increases in CD8 responses were observed in 11 patients (55%) and were characterized as follows: either at least a threefold amplification from baseline of HIV-gag-specific CD8 T cell numbers ($n = 3$ patients), or a diversification of these responses, as defined by at least one novel gag-peptide pool recognized ($n = 3$ patients), or both a threefold amplification and a diversification ($n = 5$ patients) (Fig. 3). Fig. 4 reports the kinetics and intensity of the HIV-gag-specific CD8 responses. For these 11 responders the median HIV-gag-specific CD8 cell counts increase from baseline was +946 SFC/10^6 PBMC (range: +70; +4648) ($p < 0.001$) at time of their maximal response (Fig. 4). In contrast, control EBV antigens did not show any amplification of CD8 cell frequency (data not shown), suggesting the specificity of the immunization procedure.

The Kimloch-de Loes article states the following at page 614:

> The choice of vaccine candidates for this study was dictated by their safety records in HIV-1–infected subjects, immunogenicity, and availability [20–22]. Remune was used preferentially to increase $CD4^+$ T helper cells, and ALVAC-HIV was used to increase CTLs [22–25]. The combination of vaccines in a single treatment arm was selected for its potential to enhance both components of T cell immunity. Our results demonstrate that these vaccines were immunogenic, in that they increased $CD4^+$ and $CD8^+$ T cell responses, as measured by IFN-γ ELISPOT assay, compared with the results with the placebo vaccines.

The Jin summarizes the data in the Abstract as follows:

> Of the 14 patients who completed vaccination, 13 had significant increases in anti-gp120 or anti-p24 antibody titers, and 9 had transient augmentation of their T-cell proliferation responses to gp160 and/or p24. HIV-1-specific $CD8^+$ T cells were quantified using an intracellular gamma interferon staining assay. Among 11 patients who had increased $CD8^+$ T-cell responses, seven had responses to more than one HIV-1 antigen.

Accordingly, contrary to the Examiner's allegations, Applicant has proffered new experimental evidence obtained from peer-reviewed publications that addresses the Examiner's allegations that Applicants methods are unpredictable and not reproducible.

Applicant respectfully requests withdrawal of this rejection under section 112.

Peptides

The Examiner alleges that not all HIV Gag, Gp120, Nef and Pol peptides are enabled by the specification.

Applicant submits that any one of skill in the art can select a peptide from any of the HIV Gag, Gp120, Nef and Pol proteins, insert it into an attenuated pox virus, and administer the resulting recombinant pox virus to an HIV-infected person. Moreover the art is replete with examples of HIV peptides that are immunogenic.

For example, Dorrell provides data on HIV infected patients who received HAART and a modified vaccinia virus Ankara (MVA) that expresses an immunogen,

HIVA, which includes consensus HIV-1 Gag p24/p17 sequences. Those patients exhibited CD8+ T cell responses against at least 8-10 peptides that were previously undefined as HIV epitopes (see Table 2 and page 4709, left column). Thus, the teachings of the application in conjunction with information available in the art easily allow one of skill in the art to make and use the methods of the invention.

Moreover, Tubiana discloses that the increases in CD8 responses included at least a threefold amplification from baseline of HIV-gag-specific CD8 T cell numbers, or a diversification of these responses, as defined by at least one novel gag-peptide pool recognized, or both a threefold amplification and a diversification (see, Tubiana Fig. 3 and page 4297, left column).

Thus, as shown by Dorrell and Tubiana, the CD8+ response can *diversify* to HIV peptide epitopes that were not previously recognized by the patients' immune system. These data therefore show that a variety of HIV peptides can successfully be used in the methods of the invention.

However, to expedite the allowance of the application, claim 1 is now directed to use of HIV specific peptides that consist of HIV Gag, Pol or Env peptides.

Applicant respectfully requests withdrawal of this rejection under section 112.

Guidance as to the correlates of human protection

The Examiner asserts that the specification does not provide guidance on the correlates of human protection and states that it is unclear what type of immune response is required to provide a therapeutic benefit.

Claim 1 states that the method stimulates HIV antigen-specific *CD8+ and CD4+ proliferative* responses. Applicant submits that the claims are clear as to what type of immune response is required to provide a therapeutic benefit.

The Examiner asserts that there is no experimental evidence that HIV-1-specific cellular immunity prevents disease and that CD8+ T cell responses by definition are not protective in nature.

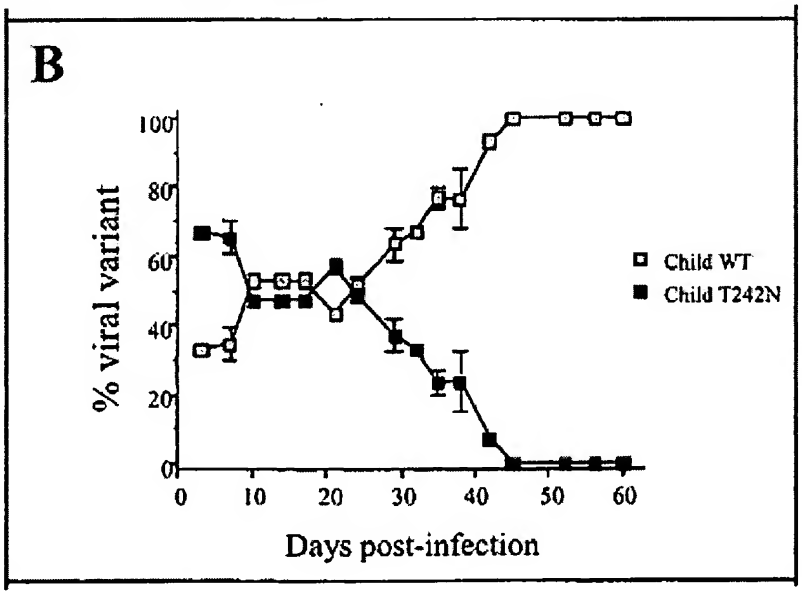
Applicant again reminds the Examiner that the terms "protection" and "prevention" are not used in the claims and requests that the Examiner focus on the language of the claimed invention rather than improperly reading a limitation from the written description into the claims.

Applicant respectfully requests withdrawal of this rejection under section 112.

Quasispecies nature of HIV

The Examiner alleges that the HIV-1 genome is plastic and contributes to immune escape, thereby preventing development of an effective vaccine.

Applicant submits that the Examiner's allegations in this regard are not necessarily true, particularly as they apply to Applicant's invention. As described by Martinez-Picado et al., HIV mutations that may contribute to immunological escape take a toll in the mutant virus in terms of fitness (J. Virol. 80(7): 3617-23 (2006) provided herewith in a Supplemental Information Disclosure Statement). This is demonstrated, for example, by Martinez-Picado's Figure 1B (reproduced below), which shows that the numbers of T242N mutant viruses quickly become reduced relative to wild type.



Accordingly, mutant viruses do not multiply as effectively as wild type viruses and are the viral load of such mutants can become insignificant with time.

In addition, as shown by Dorrell and Tubiana, the CD8+ response can *diversify* to HIV peptide epitopes that were not previously recognized by the patients' immune system. Dorrell shows that HIV infected patients exhibited CD8+ T cell responses against at least 8-10 peptides that were previously undefined as HIV epitopes (see Table 2 and page 4709, left column) when the methods of the invention are used. Tubiana discloses that the increases in CD8 responses included at least a threefold amplification from baseline of HIV-gag-specific CD8 T cell numbers, or a diversification of these responses, as defined by at least one novel gag-peptide pool recognized, or both a threefold amplification and a diversification (see, Tubiana Fig. 3 and page 4297, left column).

Thus, the inventive methods are clearly able to deal with whatever HIV-quasispecies problems may arise.

Applicant respectfully requests withdrawal of this rejection.

Working Examples

The Examiner asserts that the claims encompass considerable breadth with respect to HIV-specific peptides and viral constructs but the only examples provided in the specification are prophetic.

Claim 1 is directed to administration of attenuated recombinant *NYVAC, ALVAC or MVA* pox viruses that express *gag or env* HIV-specific peptides.

Applicant submits that the specification clearly enables this scope of viral vectors and peptides. In particular, the specification provides data (FIG. 2, page 18, line 24 to page 21, line 28) showing that HAART-treated animals who were inoculated with a recombinant NYVAC, which produces gag-pol-env HIV specific peptides (Group B), exhibited substantially increased percentages of HIV-specific $CD8^+$ T cells relative to HAART-treated animals who received a placebo vaccine (Group A) or animals inoculated with the recombinant NYVAC virus who had received no HAART treatment (Group C). Thus, as the specification discloses at page 22, lines 8-10, the inventive methods induced significant expansion of the number of CD8+/CD3+ cells specific for an immunodominant gag peptide only in animals treated effectively with antiretroviral

therapy (i.e., both anti-retroviral agents and the recombinant NYVAC virus that produces gag-pol-env HIV specific peptides).

Applicant submits that the results of these Examples and the teachings of the application have been confirmed in human patients as shown by the Franchini Declaration, and the Jin, Tubiana, Kimloch-de Loes and Dorrell publications.

Applicant respectfully requests withdrawal of this rejection under section 112 in view of the foregoing comments and the language of the claims.

CONCLUSION

Applicant respectfully submits that the claims are in condition for allowance, and notification to that effect is earnestly requested. The Examiner is invited to telephone Applicant's attorney at (516) 795-6820 to facilitate prosecution of this application.

If necessary, please charge any additional fees or credit overpayment to Deposit Account No. 19-0743.

Respectfully submitted,

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CERTIFICATE UNDER 37 CFR 1.8: The undersigned hereby certifies that this correspondence is being deposited with the United States Postal Service with sufficient postage as first class mail, in an envelope addressed to: Commissioner of Patents, P.O. Box 1450, Alexandria, VA 22313-1450, on this 6th day of June, 2008.

Patricia A. Hultman

Name

Signature